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Carriers of the Usher Syndrome Type IB: Is Audiometric Identification Possible?

M. Wagenaar, A.F.M. Snik, *W.J. Kimberling, and C.W.R.J. Cremers

*Department of Otorhinolaryngology, University Hospital Nijmegen, Nijmegen, The Netherlands, and *Boys Town National Research Hospital, Omaha, Nebraska, U.S.A.*

Some studies in the past have shown that carriers of genes for recessive deafness cannot be identified by standard audiometry. However, remarkable results with regard to the identification of heterozygotes have been reported using Békésy audiometry and Audioscan audiometry. In the present study, nine obligate carriers from five families with the Usher syndrome type IB were examined. Methods that reflect the function of the cochlea, including pure-tone audiometry, Audioscan audiometry, and otoacoustic emission measurements were used to detect (subtle) audiometric manifestations of heterozygosity. Abnormalities in hearing sensitivity were found in some obligate carriers but to the same extent in some of the controls. No statistically significant differences were found in the presence of audiometric abnormalities between carriers and controls. Additional audiologic measurements indicated that if hearing loss was present in Usher type IB carriers, it was presumably of cochlear origin. It is concluded that carriers of the Usher syndrome type IB cannot be identified properly via standard audiometric methods. **Key Words:** Usher syndrome type IB—Audiometric identification.
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The Usher syndrome is an autosomal-recessive disorder with congenital sensorineural hearing loss and retinitis pigmentosa. It was first described by a British ophthalmologist in 1914 and affects approximately three to four per 100,000 people. Three different types of the Usher syndrome can be distinguished, based on the clinical features (1). Gene analysis demonstrated that the clinical types I and II can be caused by genes on various loci (Table 1) (2–4).

Information on the carrier status might be of importance to members of a family with affected members. As long as genetic identification of carriers is not yet possible, there will be a search for tests that may identify clinically carriers of the Usher syndrome.

Throughout the years, several studies have focused on the identification of carriers of autosomal-recessive deafness using audiometric tests. Table 2 summarizes the results of carrier studies that have been performed in the past few decades. Some studies found that an autosomal-recessive gene had no influence on the hearing abilities of carriers (5–8). On other hand, other investigators described hearing impairment in excess of the age-related hearing loss in the pure-tone audiograms of carriers of several autosomal-recessive deafness syndromes (9–12). Anderson et al. (13) and, more recently, Meredith et al. (14) reported typical hearing notches in the Békésy audiograms and/or the Audioscan audiograms of these carriers. These studies suggest that more refined audiometric methods may be used to trace some degree of hearing loss in carriers. In a comparative study, Meredith et al. found that Audioscan audiometry was more sensitive than Békésy audiometry to detect notches in hearing sensitivity (14). Therefore, we focused on Audioscan audiometry and studied carriers of the Usher syndrome type IB as part of an ongoing project on the clinical and genetical aspects of the Usher syndrome type I. Because individuals with type I are more severely affected than are individuals with the Usher syndrome type II, we hypothesized that if an influence of the gene was to be measured in heterozygotes, it might be more prevalent in obligate carriers of the Usher syndrome type I than in carriers of the Usher syndrome type II. Therefore, we expected the audiometric abnormalities found in the Usher syndrome type II carriers to be even more pronounced in our study group of Usher type IB carriers. In addition to Audioscan audiometry, otoacoustic emission (OAE) measurements (15) were performed to verify the presence of hearing notches detected with Audioscan.

The origin of possible (subtle) audiometric abnormalities in the carriers of the Usher syndrome type I may

Address correspondence and reprint requests to Dr. M. Wagenaar, Department of Otorhinolaryngology, University Hospital Nijmegen, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands.

TABLE 1. *Subtypes of the Usher syndrome*

Usher syndrome type	Hearing loss	Vestibular function	Retinitis pigmentosa	Linkage
I	Severe to profound, congenital	Absent	Prepubertal	USH1A: chromosome 14q32 USH1B: chromosome 11q13.5 (myosin VIIA) USH1C: chromosome 11p13-15
II	Moderate to profound, stable or progressive, congenital	Normal	Pre-/postpubertal	USH2A: chromosome 1q14 USH2B: unlinked
III	Progressive, congenital	Variable	Pre-/postpubertal	USH3: chromosome 3q

be related to the myosin VIIa protein. Recently the Usher 1B gene was identified as coding for this protein. Myosin VIIa may be important for the motion of the stereocilia in the inner ear, but its exact function in the cochlea and retina is yet unknown. Mutations in the gene may give rise to single amino acid substitutions, which would be expected to produce an abnormal myosin VIIa, whereas mutations that truncate the message would not be expected to produce protein product. One would presume that in carriers with mutations that actually change the amino acid composition, abnormal and normal myosin VIIa protein would coexist in the cytostructure of the inner and outer hair cells and that audiologic characteristics of the Usher syndrome, albeit mild, would be predicted. In order to find audiologic evidence for the presumed cochlear origin of the hearing loss in the carriers of the Usher syndrome type IB, if present, additional measurements (speech audiometry, auditory evoked potential measurements, and stapedius reflex testing) were performed.

SUBJECTS AND METHODS

Figure 1 shows the pedigrees of the families involved in this study. Carriers are numbered 1 to 9. In two families the parents were related. Gene linkage data were available on all families, obtained from the Boys Town National Research Hospital (Omaha, NE). All pedigrees showed linkage to chromosome 11q13.5 and were therefore designated as USH1B. The obligate carriers in this study, comprising five women and four men 40–75 years of age, were the parents of one or more affected children. The diagnosis of the Usher syndrome type I in these children was confirmed by medical history and thorough otoscopical, audiovestibular, and ophthalmological examination at the University Hospital Nijmegen (UHN) (12). None of the carriers complained of hearing impairment, except for carrier 9, the oldest carrier, who was using a hearing aid. A control group comprising 25 individuals (15 women and 10 men 24–60 years of age) was recruited from the staff at the UHN. None of them had a history of hearing impairment.

Pure-tone audiometry was performed using the automated Hughson-Westlake procedure. The Audioscan audiometer (Essilor, Ltd) with Beyer Dynamic DT48 headphones was used for this purpose, calibrated according the ISO 389 (16). The method of ISO 7029 (17) was followed to calculate the P50 and P90 (50th and 90th percentiles) threshold values for presbyacusis for each carrier and control subject in relation to her or his age and sex. The individual P50 and P90 values thus obtained at 1, 2, 4 and 8 kHz are compared with the measured values. This method has been described in more detail by Robinson and Sutton (18).

All the subjects also were tested audiometrically according to the Audioscan method (14,19,20). This method makes use of frequency sweeps at a fixed level (in dB HL) to scan hearing acuity from 0.25 to 8 kHz. The sweep rate was 15 s per octave. If the tone sweep was not heard in a certain frequency region, the in-

TABLE 2. *Review of the literature on the audiometric identification of carriers of autosomal-recessive deafness*

Year	First author	Autosomal-recessive obligate carriers	Audiometry: Type	Audiometry: Results
1957	Wildervanck	Parents (n = 30)	Pure tone	NH
1966	Kloepfer	Parents/siblings (n = 28) (Usher type I)	Pure tone	Slight hearing loss
1968	Anderson	Parents (n = 60)	Békésy	Notches (17%)
1971	McLeod	Parents/siblings (n = 8) (Usher type II)	Pure tone	High frequency hearing loss
1989	Marres	Parents (n = 10)	Békésy	NH
1991	Van Rijn	Parents (n = 60)	Pure tone	NH
1992	Meredith	Parents/siblings (n = 5) (Usher type II)	Békésy	NH
			Audioscan	Notches (100%)
1995	Van Aarem	Parents/siblings (n = 10) (Usher type IIA)	Pure tone	Hearing loss

NH, normal hearing.

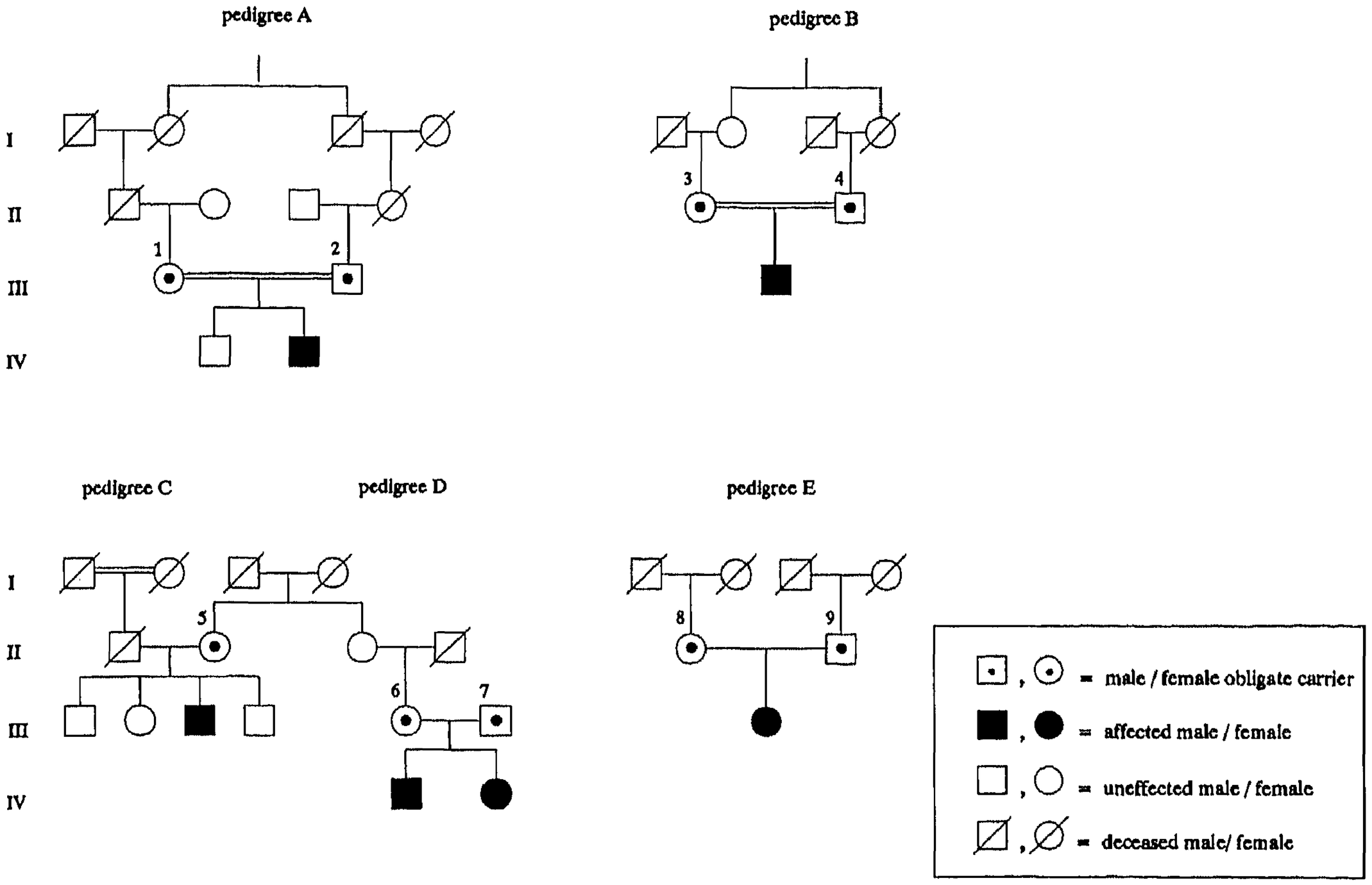

FIG. 1. Pedigrees of the five families involved in this study. Carriers are numbered 1 to 9.

tensity in that frequency region was increased automatically in 5-dB steps (19). Figure 2 shows a typical example of an Audioscan recording obtained from one of the carriers. Notches in hearing sensitivity can be identified on these recordings. A hearing notch was defined as an increase in the hearing threshold of at least 15 dB within one octave, with recovery at higher frequencies of at least 10 dB. We determined hearing notches in the frequency range of 0.5 to 3 kHz because notches in the 4-kHz range might result from noise exposure (13,14).

Cochlear function also was evaluated by means of OAEs. Although OAEs and hearing acuity are related, this relationship is not straightforward (15,21). Therefore, in the present study OAEs were only used to verify audiometrically determined hearing notches. Transient evoked OAEs (TEOAEs) were obtained using the ILO88-system (Otodynamics) (15). Unfiltered 80-µs

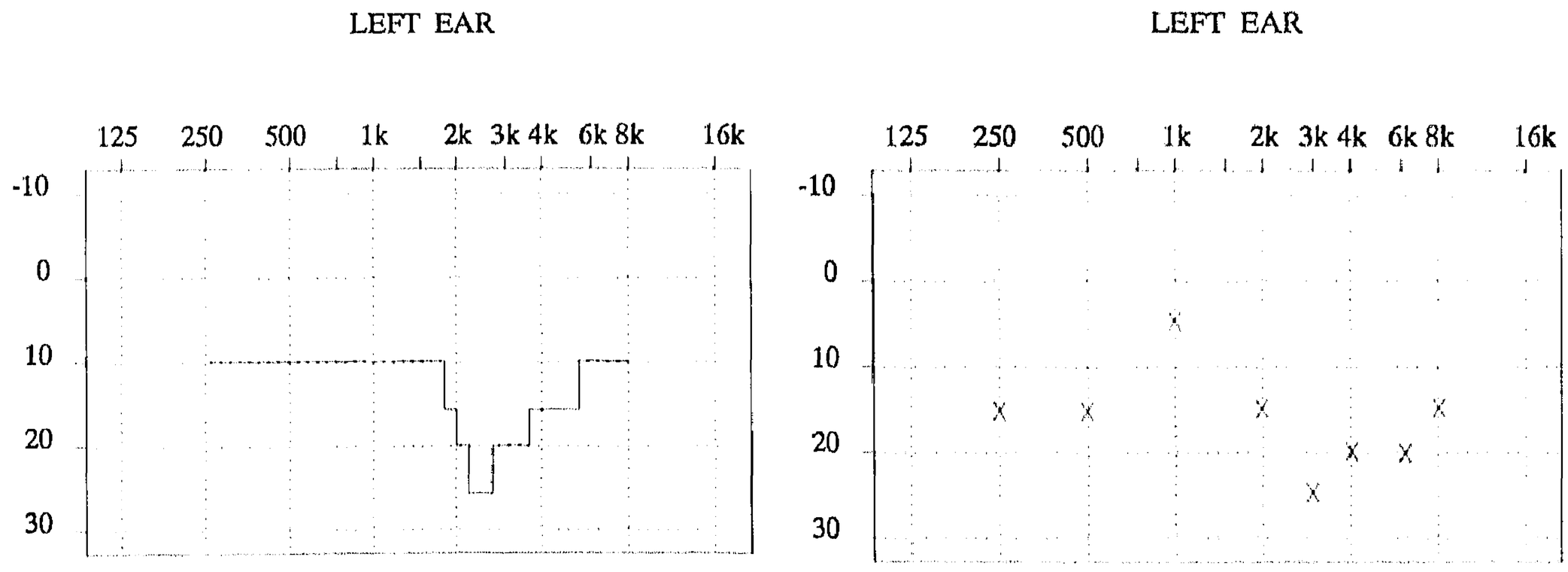

FIG. 2. **A:** Audioscan recording of the left ear of carrier 1. At ~2.5 kHz a notch in hearing sensitivity is seen. **B:** Results of pure-tone audiometry in the same ear.

clicks were used at a stimulus level of 80 dB sound pressure level (SPL) (±3 dB). The TEOAE plots were judged for the presence or absence of an OAE based on the stimulus parameters, response parameters, and spectra.

In five of the nine carriers, who had (some) hearing loss, audiometric evaluation was supplemented by speech audiometry, stapedius reflex measurements, and brain stem audiometry (ABR) to study the site of the lesion. The remaining four carriers were not included in this part of the study because hearing sensitivity was found to be normal.

Tests were performed in double-walled sound-treated rooms by the same person. Standard lists of monosyllables were used for speech audiometry. Stapedius reflex measurements with contralateral stimulation were taken using a clinical acoustic impedance meter (Amplaid 720). The test signals were pure tones of 0.5, 1, 2, and 4 kHz. In accordance with Anderson et al. (13), stapedius reflex thresholds of 100 dB hearing level (HL) or more were considered to be pathological. For the ABR measurements, electrodes were placed on the forehead and both mastoids. The ground electrode was placed on the subject's wrist. Condensation and rarefaction clicks of 70 dB normal hearing level (nHL) were applied, generated by the Medelec AS10 with a duration of 0.1 ms and a repetition rate of 15 per second. If the response quality was poor, the measurement was repeated at 80 dBnHL. Responses to 1,024 stimuli, band pass filtered (0.1–3 kHz), were averaged and stored (Medelec ER94a).

RESULTS

Results of pure tone and Audioscan audiometry in obligate carriers are presented in Table 3. In eight of the carriers, the PTA was below 20 dB HL, which indicates normal hearing. However, carriers 2, 4, 8, and 9 were found to have high-frequency sensorineural hearing loss (threshold at 4 and/or 8 kHz exceeding 20 dB HL). In carrier 8, the hearing loss was asymmetrical. In the control group, 24 of the 25 subjects had normal hearing. One subject had high-frequency hearing loss.

Next, the individual thresholds were compared with age- and sex-matched P50 values. This was done at 1, 2, and 8 kHz, and the average differences were calculated (Table 3, rows 6 and 7). The 4-kHz threshold was excluded to minimize the effect of noise-induced hearing notches. The average measured thresholds of the carriers were 2.2 dB above the P50 values with a standard deviation of 9.0 dB. This difference is not statisically significant (*t* test). (As a control, we compared measured and P50 values of our control group; on average, a difference of 2 dB was found that was considered as adequate.) On an individual level, 44% of the carrier's ears showed measured thresholds below the P50 values and 100% below P90 values.

The Audioscan method detected hearing notches in the 0.5–3 kHz range in four of the 18 ears (22%) of obligate carriers (Table 3, rows 8 and 9). However, in eight of the 50 control ears (16%) a hearing notch was also found. Because the mean age in the control group (36 years) was lower than that in the carrier group (54 years), we reevaluated these results using the data from subjects 40–60 years of age in the carrier group (n = 7; mean age 51 years) and control group (n = 8; mean age 49 years). Table 4 summarizes the results; there were no statistically significant differences in the occurrence of notches between either the whole carrier and control groups or between the age-matched carrier and control subgroups (χ^2 test, $p > 0.05$).

TEOAE measurements were introduced to verify the presence of audiometrically determined hearing notches. The spectra of the OAE of carriers 1 and 4, who had a hearing notch according to Audioscan audiometry, were examined. No reproducible response was found between 2.2 and 4.3 kHz in either ear of carrier 1 and between 2.3 and 3.6 kHz in either ear of carrier 4. These results are in accordance with the notch region found by Audioscan audiometry.

Next, a comparison was made of the TEOAE response of the carriers 40–60 years of age and a control group of age-matched subjects with normal hearing taken from our database (unpublished observations). The result is

TABLE 3. *Results of pure-tone audiometry and Audioscan audiometry in obligate carriers of the Usher syndrome*

			PTA (dB HL) (0.5, 1, 2 kHz)		Measured threshold minus P50 (dB HL) (1, 2, 8 kHz)		Depth notches (dB HL)	
Carrier	Sex	Age (yr)	AD	AS	AD	AS	AD	AS
1	F	40	12	12	+2	+7	15	15
2	M	45	7	3	+3	+6	—	—
3	F	51	10	2	+5	−5	—	—
4	M	53	18	13	+3	−2	55	30
5	F	59	8	3	−6	−16	—	—
6	F	49	15	5	+5	−2	—	—
7	M	53	8	3	−2	−9	—	—
8	F	65	8	18	−2	+20	—	—
9	M	75	25	22	+17	+15	—	—

AS, left ear; AD, right ear; —, no notch in hearing sensitivity found.

TABLE 4. *Occurrence of notches in hearing sensitivity using Audioscan audiometry in obligate carriers and controls*

Group	Ears	Occurrence of notches
Carriers	18	4 (22%)
Controls	50	8 (16%)
Carriers (40–60 yr)	14	4 (28%)
Controls (40–60 yr)	16	4 (25%)

presented in Table 5. Literature values on a population of subjects with normal hearing in the same age range have been added (21). No statistically significant differences were found between the three groups.

In carriers 1 and 4, who had a notch in hearing sensitivity, and carriers 2, 8, and 9, who had high-frequency hearing loss, additional audiometry was performed to verify the origin of the hearing loss, or, more specifically, to determine whether there were signs of retrocochlear involvement or middle ear problems. Speech reception scores were evaluated in relation to the pure-tone thresholds, as described by Gates et al. (22). In all the carriers tested, the speech reception scores were within 1 SD of the calculated values based on pure-tone thresholds, which suggested that speech reception was in accordance with the level of hearing loss without suspicion of neural involvement. Tympanometry showed normal middle ear pressure and compliance in all five carriers.

The stapedius reflex was elicitable at normal levels in four of the five carriers. In carrier 9, no stapedius reflex could be elicited up to 120 dB HL. ABR showed reproducible responses with normal wave I–V intervals in all five carriers tested.

DISCUSSION

Pure-tone audiometry showed that most of the carriers had hearing thresholds that were close to age-related normative values (Table 3, rows 6 and 7). There was a tendency in the elderly carriers (8 and 9) to have hearing loss in excess of the P50. This seems to be in agreement with findings of other studies, which suggest that the cochleae of heterozygotes of the Usher syndrome might be more susceptable to degenerative processes and/or exogenous influences (9–11).

With use of Audioscan audiometry, hearing notches were detected in Usher type IB carriers, but the prevalence did not differ from that found in the control group. Hearing notches were found in 22% of the carriers. A similar figure was reported by Anderson et al. (13), who examined carriers of autosomal-recessive deafness using Békésy audiometry, whereas Meredith et al. (14) found notches in 100% of the obligate carriers of the Usher syndrome type II using the Audioscan method. Differences between the results of this study and the study performed by Meredith et al. (14) might be due to the fact that two populations with different diagnosis, namely, Usher type II and type I heterozygotes, were studied. The two types are genetical distinct, and type I is more severe. We hypothesized that the influence of an Usher gene in carriers of the Usher syndrome type IB would be more prominent than in carriers of type II, but this did not seem to be the case.

If we assume that the Usher gene affects cochlear function, then abnormalities are to be expected in tests that reflect the function of the cochlea but not in tests that reflect the retrocochlear or middle ear function, as was found in this study. The only exception was carrier 9, in whom no stapedius reflex could be elicited. Nevertheless, retrocochlear involvement seems unlikely because of reproducible and normal ABR results. In their study, Anderson et al. (13) also found abnormal stapedius reflex thresholds, even in the majority of their possible carriers. They had no explanation for this observation and, in later studies, this finding could not be confirmed (8,11,12). Therefore, the absence of the stapedius reflex in carrier 9 remains unexplained.

To conclude, notches in hearing sensitivity were not more common in the carriers of the Usher syndrome type IB than in the control subjects. If hearing loss was present, it was most probably of cochlear origin.

Although the number of carriers is limited, a clinically relevant conclusion can be drawn. Carriers of the Usher syndrome type IB do not show characteristic audiometric abnormalities that would enable their identification by standard audiometric testing.

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TABLE 5. *TEOAE response of the carriers and controls within the same age range*

Study	Group	Ears	TEOAE response (dB SPL)[a]
Present	Carriers	14	8.4 ± 2.9
Present	Controls	34	9.0 ± 4.6
Robinette (21)		97	8.3 ± 5.0

Participants were all 40–60 years of age. Literature results are added (subjects with normal hearing and within the same age range).

[a]Means ± SD.

REFERENCES

1. Kimberling WJ, Möller C. Clinical and molecular genetics of Usher syndrome. *J Am Acad Audiol* 1995;6:63–72.
2. Weil D, Blanchard S, Kaplan J, et al. Defective myosine VIIA gene responsible for Usher syndrome type 1B. *Nature* 1995;374:60–1.
3. Smith RJH, Lee EC, Kimberling WJ, et al. Localization of two genes for Usher syndrome type I to chromosome 11. *Genomics* 1992;14:995–1002.
4. Kaplan J, Gerber S, Bonneau D, et al. A gene for Usher syndrome type I (USA1A) maps to chromosome 14q. *Genomics* 1992;14:979–87.

5. Wildervanck L. Audiometric examination of parents of children deaf from birth. *Arch Otolaryngol* 1957;65:280–95.
6. Fraser GR. A study of causes of deafness amongst 2,355 children at special schools. In: Fisch L, ed. *Research into causes of deafness in children*. Oxford, England: Blackwell, 1964: 10–3.
7. Marres HAM, Cremers CWRJ. Autosomal recessive nonsyndromal profound childhood deafness in a large pedigree. Audiometric features of affected persons and the obligate carriers. *Arch Otolaryngol Surg* 1989;115:591–5.
8. Van Rijn PM, Cremers CWRJ. Causes of childhood deafness at a Dutch school for the hearing impaired. *Ann Otol Rhinol Laryngol* 1991;100:903–8.
9. Kloepfer HW, Laguaite JK, McLaurin JW. The heriditary syndrome of congenital deafness and retinitis pigmentosa (Usher's syndrome). *Laryngoscope* 1966;76:850–62.
10. McLeod AC, McConnell FE, Sweeney A, Cooper MC, Nance WE. Clinical variation in Usher's syndrome. *Arch Otolaryngol* 1971;94:321–34.
11. Van Aarem A, Cremers CWRJ, Pinckers AJLG, Huygen PLM, Hombergen GCJH, Kimberling BJ. The Usher syndrome type 2A: clinical findings in obligate carriers. *Int J Pediatr Otorhinolaryngol* 1995;31:159–74.
12. Wagenaar M, Ter Rahe B, Van Aarem A, et al. Clinical findings in obligate carriers of type I Usher syndrome. *Am J Med Genet* 1995;59:375–9.
13. Anderson H, Wedenberg E. Audiometric identification of normal hearing carriers of genes for deafness. *Acta Otolaryngol* 1968;65:535–54.
14. Meredith R, Stephens D, Sirimanna T, Meyer-Bisch C, Reardon W. Audiometric detection of carriers of Usher's syndrome type II. *J Audiol Med* 1992;1:11–9.
15. Kemp DT, Ryan S, Bray P. A guide to effective use of otoacoustic emissions. *Ear Hear* 1990;11:93–105.
16. ISO 389. *Acoustics—standard reference zero for the calibration of pure-tone air conduction audiometers*. Geneva: International Organization for Standardization, 1985.
17. ISO 7029. *Acoustics—thresholds of hearing by air conduction as a function of age and sex for otologically normal persons*. Geneva: International Organization for Standardization, 1984.
18. Robbins DW, Sutton GJ. Age effect in hearing. A comparative analysis of published threshold data. *Audiology* 1979;18:320–34.
19. Meyer-Bisch C. Audiométrie automatique de dépistage préventif: le balayage fréquentiel asservi (Audioscan). *Cahier Notes Doc* 1990;139:335–45.
20. Lina-Granade G, Chery-Croze S, Collet L, Morgon A. Audioscan (High-definition automatic audiometry); clinical interest. *J F ORL* 1994;43:191–6.
21. Robinette MS. Clinical observations with transient evoked otoacoustic emissions with adults. *Semin Hear* 1992;13:23–35.
22. Gates GA, Popelka GR. Neural presbyacusis: a diagnostic dilemma. *Am J Otol* 1992;13:313–7.